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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/810,670	03/19/2001	Akiko Itai	P20797	9032

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EXAMINER

MORAN, MARJORIE A

ART UNIT	PAPER NUMBER
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1631

DATE MAILED: 09/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/810,670	<b>Applicant(s)</b> ITAI ET AL.	
	<b>Examiner</b> Marjorie A. Moran	<b>Art Unit</b> 1631	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 14 November 2001.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-8 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-8 is/are rejected.
- 7) ☒ Claim(s) 1-3 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 14 November 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. 09/068,459.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>11/01; 7/02</u> . | 6) <input type="checkbox"/> Other: _____  |

### ***Information Disclosure Statement***

The information disclosure statement filed 7/3/02 has been considered in full.

The information disclosure statement filed 11/14/01 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because a copy of each cited document is not supplied with the IDS and/or is not found in the cited parent application. Reference no. 5, by Tomioka et al., reference no. 39, by Yamada et al., and two foreign references were not supplied with the IDS and are not found in the parent application.. Reference no. 28, by Sadowski et al. is a duplicate of citation no. 19 and has been crossed out to avoid duplication upon printing. The IDS filed 11/14/01 has been placed in the application file, but all the information referred to therein has not been considered as to the merits. Only the initialed references have been considered. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

### ***Claim Objections***

Claims 1-3 are objected to because of the following informalities.

Claim 3 recites the phrase "containing, at least" in line 2. As the term "containing" is open claim language (see below), the phrase "at least" is redundant and

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should be deleted. Applicant is encouraged to use standard claim terminology; it is recommended that the entire phrase "containing, at least" be replaced with -- comprising-- in claim 3. In claims 1-3, the phrase "by using a computer" in line 3 of each claim is awkward. If applicant intends a computer-implemented method, then this rejection may be overcome by amending the preamble of each claim to recite -- A computer-implemented method-- and by deleting the phrase "by using a computer" in line 3 of each claim.

Appropriate correction is required.

### ***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-7 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-7 are directed to methods for selecting lead-candidate compounds capable of binding to a biopolymer, then recite apparent steps of docking or "fitting" a putative ligand to a biopolymer. These steps are ones of mathematical manipulation, equivalent to mental processes. Where a claim recites mental processes in the absence of a concrete, tangible and useful result, the claim is not directed to statutory subject matter. See MPEP 2106 as follows:

MPEP 2106.II.A

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The claimed invention as a whole must accomplish a practical application. That is, it must produce a "useful, concrete and tangible result." *State Street*, 149 F.3d at 1373, 47 USPQ2d at 1601-02. The purpose of this requirement is to limit patent protection to inventions that possess a certain level of "real world" value, as opposed to subject matter that represents nothing more than an idea or concept, or is simply a starting point for future investigation or research (*Brenner v. Manson*, 383 U.S. 519, 528-36, 148 USPQ 689, 693-96); *In re Ziegler*, 992, F.2d 1197, 1200-03, 26 USPQ2d 1600, 1603-06 (Fed. Cir. 1993)).

#### MPEP 2106.IV.B.1

If the "acts" of a claimed process manipulate only numbers, abstract concepts or ideas, or signals representing any of the foregoing, the acts are not being applied to appropriate subject matter. *Schrader*, 22 F.3d at 294-95, 30 USPQ2d at 1458-59. Thus, a process consisting solely of mathematical operations, i.e., converting one set of numbers into another set of numbers, does not manipulate appropriate subject matter and thus cannot constitute a statutory process.

#### MPEP 2106.IV.B.2 (b) ii

A process that merely manipulates an abstract idea or performs a purely mathematical algorithm is nonstatutory despite the fact that it might inherently have some usefulness. In *Sarkar*, 588 F.2d at 1335, 200 USPQ at 139, the court explained why this approach must be followed: No mathematical equation can be used, as a practical matter, without establishing and substituting values for the variables expressed therein. Substitution of values dictated by the formula has thus been viewed as a form of mathematical step. If the steps of gathering and substituting values were alone sufficient, every mathematical equation, formula, or algorithm having any practical use would be per se subject to patenting as a "process" under 101. Consideration of whether the substitution of specific values is enough to convert the disembodied ideas present in the formula into an embodiment of those ideas, or into an application of the formula, is foreclosed by the current state of the law. For such subject matter to be statutory, the claimed process must be limited to a practical application of the abstract idea or mathematical algorithm in the technological arts. See *Alappat*, 33 F.3d at 1543, 31 USPQ2d at 1556- 57 (quoting *Diamond v. Diehr*, 450 U.S. at 192, 209 USPQ at 10). See also *Alappat* at 1569, 31 USPQ2d at 1578-79 (Newman, J., concurring) ("unpatentability of the principle does not defeat patentability of its practical applications") (citing *O'Reilly v. Morse*, 56 U.S. (15 How.) at 114-19). A claim is limited to a practical application when the method, as claimed, produces a concrete, tangible and useful result; i.e., the method recites a step or act of producing something that is concrete, tangible and useful. See *AT&T*, 172 F.3d at 1358, 50 USPQ2d at 1452.

None of the methods recite any physical method step (i.e. a "safe harbor") nor any step of transforming data which would render the claims statutory. It is unclear what the actual result of the claimed methods is intended to be (see below), therefore

the claims do not recite a concrete, tangible and useful result. For these reasons, the claimed methods are not statutory.

Claims 1-7 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The claims are directed to methods for selecting lead-candidate compounds capable of binding to a biopolymer, but claims 1-7 fail to actually recite any selection step. As no compound is actually selected, the claims do not produce an “immediately useful” result. In addition, a method to select a lead-candidate compound capable of binding to a biopolymer MAY be useful if one were apprised of the “use” of either such a compound or of the biopolymer itself. For example, knowledge that a compound is capable of binding an enzyme in a manner similar to that of other inhibitors provides an immediately useful result; i.e. that the “lead-candidate” is a possible inhibitor.

Knowledge that a compound binds to a biopolymer in a manner similar to that of other known drugs is useful in identifying drug candidates (e.g. out of a pool of combinatorial peptides) for further evaluation. Knowledge that a compound binds to a nucleic acid at a particular regulatory site is useful in identifying a compound as one for further evaluation as a compound which inhibits transcription, activation, etc. of nucleic acids. It is noted that in these examples, the further evaluation is one of **confirming** the activity of a compound as it relates to a **known** biopolymer. By contrast, knowledge that a compound is capable of binding a protein or nucleic acid of unknown function, and/or to a site with unknown function, is not useful. What is the “immediate benefit” to

one of skill in the art of determining that compound binds to a random site on an unidentified biopolymer? Applicant is reminded that a "use" to do further research is not a utility under 35 USC 101. Thus, although claim 8 does recite a selection step, the result of the selection step is still not one which imputes utility. For the reasons set forth above, the claims lack utility.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are not enabled for SELECTION of a lead-candidate compound which binds to any type of biopolymer because neither the specification nor the prior art teach specific parameters for selection of a compound or compounds which bind to any (generic) biopolymer.

Claims 1-8 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for identifying compounds which may bind to proteins such as dihydrofolate reductase, does not reasonably provide enablement for identifying compounds which bind to any other type of biopolymer. The specification does not

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enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Where the claims read on merely identifying compounds capable of binding to a biopolymer, the claims are enabled for identifying compounds which may bind to proteins such as dihydrofolate reductase because the specification teaches how to perform docking assays with proteins found in structural databases such as the Cambridge Crystallographic Database (CCD) or the Brookhaven Protein Data Bank (PDB), but are not enabled for identifying compounds which bind to any other type of biopolymer because neither the specification nor the prior art teach how to do so.

The factors to be considered in determining what constitutes undue experimentation were affirmed by the court in *In re Wands* (8 USPQ2d 1400 (CAFC 1986)). These factors are the quantity of experimentation; the amount of direction or guidance presented in the specification; the presence or absence of working examples; the nature of the invention; the state of the prior art; the level of skill of those in the art; predictability or unpredictability of the art; and the breadth of the claims.

The claims are quite broad as they are directed to selection of a lead-candidate compound capable of binding any type of biopolymer. The claims may also be interpreted broadly as merely identifying compounds which bind to a biopolymer. The specification teaches, in examples, how to determine/identify compounds likely to bind to a protein, specifically dihydrofolate reductase. The specification does not teach particular conditions which must be met to select a compound as a "lead-candidate"; i.e. to single out any particular compound as being a "better" ligand than the others, or which binds more tightly than another, etc. The state of the prior art is such that docking programs for "fitting" a ligand into a binding site of a protein are known. See



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e.g. DESJARLAIS et al. (IDS ref: J. Med. Chem. (1988) vol. 31, pp. 722-729).

DESJARLAIS teaches specific steps for “scoring” the fit between a receptor and candidate compounds and teaches on page 724 that a user may “select the number of top scoring candidates” to be saved for further energy minimization steps. It is noted that the claimed methods do not recite any particular steps of scoring or ranking candidate compounds similar to those of DESJARLAIS, such that a selection may be made of the “top” candidates. It is further noted that DESJARLAIS teaches fitting only to proteins wherein the crystallographic structure is known (pp. 726-727). The prior art of NISHIBATA (IDS ref: Tetrahedron (1991) vol. 47, no. 43, pp. 8985-8990) teaches design of drug candidates based on the KNOWN structure of protein receptors using the LORE program. Again, NISHIBATA teaches use of a protein with known crystallographic coordinates (p. 8987) and does not teach design of candidate compounds which bind to any other type of biopolymer. In addition, NISHIBATA teaches specific parameters for selection of nine “lead-candidate” structures from among the 300 possible structures generated (pp. 8987-8989). The instant specification teaches “use” of similar parameters (e.g. information about atomic types and mode of covalent bonding), but fails to disclose any specific parameters which would allow one of skill in the art to know WHAT to select. For example, what kind of “atomic types” are to be excluded or included in the selection step? Which covalent bonds are to be considered? Are certain types of bonds excluded, included, or perhaps weighted? Claim 1 recites that “stability of complex structures” is to be used as a criteria for judgment. However, neither the instant claims nor the specification disclose

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which parameters are to be used to determine stability. As set forth in the prior art, *supra*, there are many parameters which may be included in a "stability" determination, and at least some of those are particular to the biopolymer and/or algorithm chosen for the docking/fitting determination.

The level of skill in the art of docking/fitting is acknowledged to be high. Despite this. It would require undue experimentation for one of skill in the art to identify any compound capable of binding to a biopolymer other than a protein because such a method is not taught by the instant specification of the prior art, as set forth above. Further, it would require guesswork by a skilled practitioner to determine how to *select* a "lead-candidate" capable of binding to a protein or any other type of biopolymer because neither the specification nor the prior art teach conditions or parameters for selection which are universal to all biopolymers. Conditions for determining the "best" or "lead" compounds depend on which algorithm is used, what type of protein is chosen, and what type of activity one is looking for in a "lead" compound (i.e. binding alone? tightness of fit? lowest energy? similarity to other (known) drugs? etc.) As one of skill in the art would have to guess at the parameters involved in selection, this would require undue experimentation.

For the reasons set forth above, the claims are not enabled for selection of lead-candidate compounds of any type, and are enabled only for identification of compounds capable of binding to proteins, but not to any other type of biopolymer.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Examiners note: The term "containing" recited in the claims is interpreted to be open claim language, equivalent to --comprising--.

Claims 1-2 provides for the use of a computer, but, since the claim does not clearly set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 1-2 are also rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

As the steps intended in claims 1-2 are unclear, the claims will be interpreted as if they recite the same steps as claim 3, for purposes of search and applying the prior art.

Claims 1-2 are directed to methods of “selecting” compounds, but fail to recite any actual selection step or steps, therefore it is unclear what method applicant actually intends. Claims 3 and 8 recite steps of “selection” but fail to recite any criteria or parameters for performing a selection (e.g. what is selected for or against?), therefore all of the claims are indefinite as it is unclear what is actually being selected. As the actual steps recited appear to be those of in-silico binding or fitting/docking between a biopolymer and candidate compounds, for purposes of search and applying the prior art, the claims are interpreted to be reciting methods of docking.

Claims 1-2 recite that compounds are “modified to an extent” that binding is not to a biopolymer “is not retarded”. It is unclear what type or level of modification is intended; i.e. modification of glycosylation sites/levels, post-translational processing, deletions, insertions, substitutions, some combination of the preceding, etc. As the metes and bounds intended by applicant for the “extent” of “modification” of a compound are unclear, the claims are indefinite.

Regarding claim 2, the phrase “and the like” renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by “and the like”), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d).

Claim 6 limits a step (a) to comprise steps (c) and (d); however, no step (b) is recited. It is unclear if the claims are missing an intermediate step (b), therefore claim 6 is indefinite. It is noted that claim 5 recites a step (b); however, claim 6 does not

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depend from claim 5. In addition, the step (b) of claim 5 presumable follows step (a) whereas steps (c) and (d) are clearly limited to be part of step (a).

Claim 8 limits the method of claim 3 to further comprise a "third screening" comprising a step (f) and/or a step (g). As claim 3 recites only a step of selecting and does not recite any step of screening, it is unclear what is meant by the "third screening" limitation of claim 8, therefore claim 8 is indefinite. Further, claim 3 recites only a step (a). Recitation of steps (f) and (g), with no other intervening steps, in claim 8 renders it unclear whether other steps are intended, or are missing, from the claims, therefore claim 8 is further indefinite.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-8 are rejected under 35 U.S.C. 102(b) as being anticipated by DESJARLAIS et al. (IDS ref: PNAS (1990) vol. 87, pp. 6644-6648).

DESJARLAIS teaches a computer-implemented method of structure based drug design of inhibitors (lead-candidate compounds) of HIV-1 protease (biopolymer) wherein DESJARLAIS obtains 3D information for both the protease and drug candidates from a database and fits the drug candidates into a model of the inhibitor

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binding site of the protein (p. 6644 and Methods and Results). The compounds of DESJARLAIS are "modified" by energy minimization and orientation relative to the binding site, thus binding is "not retarded" and claims 1-5 are anticipated. DESJARLAIS teaches use of interatomic distances and covalent bonding to judge stability and "goodness of fit" (p. 6645 and Figure 1) and matches atoms to those of the query molecule (p. 6645), thus anticipating claims 6-8.

Claims 1-8 are rejected under 35 U.S.C. 102(b) as being anticipated by MOON et al. (IDS ref: Tetrahedron Computer Methodology (1990) vol. 3, no. 6C, pp. 697-711).

MOON teaches a computer-implemented method (GROW) for identifying lead compounds which are capable of binding to a receptor site of a known protein (abstract). The GROW algorithm uses atomic coordinate data and a seed structure (query) from which to initiate growth of other (modified candidate) compounds (p. 698) and teaches that atomic structural information is taken from a library (database). The "goodness of fit" and stability of compounds are evaluated using a molecular mechanics scoring function which incorporates various covalent and non-covalent interactions and inherently includes parameters such as number of atoms, number of bonds and structural details (p. 698). MOON further teaches correspondence of atoms between candidates and the query molecule (p. 699) and teaches selection steps (p. 700 and Figure 3), thus all claims are anticipated.

**Conclusion**

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (571) 272-0720. The examiner can normally be reached on Mon. to Wed, 7:30-4; Thurs 7:30-6; Fri 7-1 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571)272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marjorie A. Moran  
Primary Examiner  
Art Unit 1631

*Marjorie A. Moran*  
9/20/04